IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(s):	Patrick Cornelis Nicolaas Rensen	CONF. NO.	7547
SERIAL NO.:	10/519,417	ART UNIT:	1645
FILING DATE:	12/22/2004	EXAMINER:	HINES, JANA A
TITLE:	PREVENTION, THERAPY AND PROGNOSIS/MONITORING IN SEPSIS AND SEPTIC SHOCK		
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MAIL STOP APPEAL BRIEF
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

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REAL PARTY IN INTEREST

The applicant inventors have assigned their entire right, title and interest to Nederlandse Organisatie voor toegepast-natuurwetenschappelijk Onderzoek TNO.

RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to appellant, the appellant's legal representative, or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

STATUS OF CLAIMS

Claims 1-16 and 21 have been cancelled. Claims 19-20, 29 and 33 are withdrawn from consideration as being directed to a non-elected invention. Claims 17-18, 22-28, and 30-32 are currently active in the application and are the subject of this appeal.

STATUS OF AMENDMENTS

There are amendments to the claims after final rejection. These proposed amendments were made by amendment dated November 24, 2008 and were entered by the examiner pursuant to an Advisory Action dated January 5, 2009. It is believed that the amendments to the claims obviated the 35 U.S.C. § 112, second paragraph rejection although this was not expressly stated by the examiner in the advisory action.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention provides means for the therapeutic prevention and treatment of sepsis and septic shock by increasing the immune response of a mammal.

The sole independent claim, claim 27, is directed to a method for treating a mammal suffering from or which is at risk of developing sepsis or septic shock comprising administering to such mammal a therapeutically effective amount (page 18, line 30 to page 19, line 15) of a peptide and pharmaceutically acceptably adjuvants (page 18, lines 26-28) where the peptide (page 15, lines 14-20) comprises an amino acid sequence selected from SEQ ID NO.:11,(page 17, lines 2-5) SEQ ID NO.:2 (page 12, lines 17-19; page 16, lines 19-25) and SEQ ID NO.:1. (page 6, line 32 to page 7, line 1; page 17, lines 5-8)

GROUNDS FOR REJECTION TO BE REVIEWED ON APPEAL

Issue 1. Are Claims 17-18, 22-28, and 30-32 indefinite pursuant to 35 U.S.C. § 112, second paragraph?

Issue 2. Does Quarfordt et al., J. of Biological Chem. 1982. Vol. 257(24): 14642-14647 anticipate Claims 18, 22, 23, 25, 27-31 under 35 USC § 102(b)?

Issue 3. Does Oosten et al., (J. of Biol. Chem. 2001. Vol. 276(23): 8820-8824) in view of Quarfordt et al., (J. of Biological Chem. 1982. Vol. 257(24): 14642-14647) render Claims 17-18 and 22-32 unpatentable under 35 U.S.C. 103(a)?

ARGUMENT

Issue 1. Are Claims 17-18, 22-28, and 30-32 indefinite pursuant 35 U.S.C. § 112, second paragraph?

Applicant believes this rejection was overcome by the amendments filed in the after final response but is being responded to in this Appeal Brief for the sake of completeness of response.

Claims 17-18, 22-28 and 30-32 stand rejected under 35 U.S.C. 112, second paragraph, in that the preamble of claim 27 is unclear because claim 27 was drawn to treating a mammal suffering from or is at “increased” risk of developing sepsis or septic shock.

It was unclear to the examiner whether the method is drawn to treating a mammal suffering from a risk of developing sepsis or septic shock, or if the method treats a mammal suffering from sepsis or septic shock.

The claims in question are drawn to a method of treating a mammal suffering from a risk of developing sepsis or septic shock and to a method of treating a mammal suffering from sepsis or septic shock. The two methods are alternative since an animal already suffering from sepsis or septic shock cannot be at risk of developing something it already has.

The rejection was further based on the inclusion of the word “increased” in the phrase "at increased risk of developing sepsis or septic shock" in claim 27 since “increased” is a relative term which renders the claim indefinite.

Applicant deleted the word “increased” to obviate the basis for this rejection.

Claim 30 claims the peptide comprising SEQ ID NO:2. Claim 31 claims the peptide having the amino acid sequence of SEQ ID NO:2. The difference between the claims was unclear to the examiner what are since both claims recited "open" language.

Claim 30 is intended to encompass peptide which are, in whole or in part, SEQ ID NO:2. Claim 31 is intended to encompass only those compositions where the peptide portion is identical to SEQ ID NO:2.

Claim 31 was amended to clarify its meaning.

It is believed that the amendments to the claims incorporated in applicant’s after final response and entered by the examiner obviate these bases for rejection.

Issue 2. Does Quarfordt et al., J. of Biological Chem. 1982. Vol. 257(24): 14642-14647 anticipate Claims 18, 22-23, 25 and 27-31 under 35 USC § 102(b?)

a) The Reference

Claims 18, 22, 23, 25, 27-31 stand rejected under 35 U.S.C. 102(b) as being anticipated by Quarfordt et al., J. of Biological Chem. 1982. Vol. 257(24): 14642-14647.

The reference is cited as teaching purifying human apolipoproteins, including apolipoprotein CI (apoCI) where the apoCI has the sequences of applicant's claims 27-28.

The reference is further cited as teaching administering apoC apoproteins with pharmaceutically acceptable adjuvants by perfusion to the liver of a mammal [rats] where Table I shows the injected activity of perfused apoC-I in combination with apolipoprotein E is significantly less than that of C-III-2 and somewhat better than that of C-II in lipid recovery.

The reference is also cited as teaching preparations of pharmaceutical compositions comprising triglyceride emulsions having ApoCI.

Therefore the examiner concludes the reference teaches the instant claims.

b) Applicant's claim 27

Clim 27 is directed to method which requires the following elements:

1. administration of a
2. therapeutically (sepsis or septic shock reducing) effective amount
3. with adjuvants

4. of SEQ ID NO. 1, 2 or 11

c) Comparison of Prior Art and Applicant's Claim

1. In terms of administration, the reference discloses only perfusion into the liver of a mammal. It does not disclose intravenous injection. Liver perfusion cannot deliver a therapeutically effective amount of the active component of applicant's composition to the mammal.

2. In terms of therapeutically effective amount, there is no disclosure of that amount in the reference. There is also no disclosure that any amount, no matter how administered, would be an effective sepsis or shock reducing amount. The reference does not disclose methods of treatment - for any disease state - it only describes perfusion of a mouse liver with a solution comprising apoC-I (thereby influencing hepatocytes) and application of such a solution to a cell culture of erythrocytes.

From pages 16 and 17 of the applicant's specification, it is clear that neither of these 'uses' of apoC1 is within the scope of applicant's claims for therapeutic treatment.

On page 18 of applicant's specification under the heading "C. Administration Forms and Routes." intravenous and oral administration are disclosed.

Further, there is a difference in the dose amounts. For the perfusion liquid, the reference does not disclose the concentration of the apolipoprotein. In the cell culture experiments the reference used a concentration of 10 µg/ml.

In the present specification applicant discloses that a suitable dose of a single intravenous injection would be between 20 µg/kg and 200 mg/kg, (page 19, lines 8-9) while for a

continuous infusion a concentration of 10 µg/kg/minute to 10 mg/kg/minute can be applied. (page 19, lines 14-15)

Although, due to the difference in administration route, these closes are not fully comparable, it appears that the reference discloses such a low dose that it falls outside the range contemplated in applicant's specification and is therefore non-functional for the presently claimed purpose.

Further, it appears that the concentration used in the reference is also less than the normal plasma concentration of apoCl in sepsis patients which is 1.6 mg/dL (page 15, line 27) equal to 160 µg/ml. The doses contemplated in the instant application for a person of 70 k) would be more than 1400 µg, or an infusion of more than 700µg/minute, clearly beyond the plasma concentration.

3. The adjuvants suitable for liver perfusion would be different from those used for intravenous injection as the means of administration.

4. The reference discloses a genus various species which includes the species utilized and claimed by applicant but does not disclose the utility of applicant's species for applicants claimed method and, even further, discloses applicants claimed species as lacking high effectiveness for the different purpose disclosed by the reference.

As stated by the examiner, the reference discloses the results of administering C apolipoproteins (the genus) by perfusion (only) to rat livers (not intraveneously) and demonstrates the effect on triglyceride metabolism (not effectiveness against sepsis or septic shock). The reference treats all the livers with each of 3 C apolipoproteins, with or

without apolipoprotein E, and notes that C-III-2 (not C-I) had the greatest inhibitory effect.

In summary, the reference discloses that the composition of apoCI is known, and that it is a member of the group of apolipoproteins comprising C-I, C-II, C-III and E.

However, the reference does not disclose, explicitly or inherently, applicant's method of mitigating shock or sepsis responses in a mammal.

d) The Applicable Law

It is not in dispute that he reference does not expressly disclose all the elements of applicant's method claim. Therefore the examiner relies on the doctrine of inherency and applies the doctrine that a well known process of administration of a well known composition does not become patentable upon the discovery of a new property for that same composition citing *Atlas Powder Co. v. lreco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999) and *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977) for the proposition that claiming a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable.

However, a key antecedent to the application of the doctrine of inherency is that the "characteristic is a necessary feature or result of a prior-art embodiment...") *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)[emphasis supplied]

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*,

9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art).

To establish inherency, the extrinsic evidence "… must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981)*.[emphasis supplied]

Also, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species.

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)

e) Application of the Law to the Facts of This Case

Applying the precedents to the facts of the present case, the reference discloses the genus of apolipoproteins of which applicant's claimed species is a member. Applicant's disclosed and claimed species have a property not present in all the members of the genus and are used in a novel process where the usefulness of the claimed process depends on the provision of a therapeutically effective sepsis or shock reducing amount of the claimed species.

The determination that there is a shock reducing amount of the specifically claimed species of the known genus is not within the ability of one skilled in the art because, absent hindsight knowledge of the fact that the claimed species is effective for the claimed purpose of ameliorating sepsis or shock, the skilled practitioner would not even be led to do the experiments, however simple or complicated, to determine the parameters of the process.

Thus, applicant believes the examiner has not demonstrated that all the elements of the claimed process were disclosed by by the reference (*inter alia*, claimed species, shock reducing amount, injection instead of perfusion) and respectfully requests that the Board overturn this ground for rejection.

Issue 3. Does Oosten et al., (J. of Biol. Chem. 2001. Vol. 276(23): 8820-8824) in view of Quarfordt et al., (J. of Biological Chem. 1982. Vol. 257(24): 14642-14647) render Claims 17-18 and 22-32 unpatentable under 35 U.S.C. 103(a)?

Claims 17-18 and 22-32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Oosten et al., (J. of Biol. Chem. 2001. Vol. 276(23): 8820-8824) in view of Quarfordt et al., (J. of Biological Chem. 1982. Vol. 257(24): 14642-14647).

As cited by the examiner Oosten et al., teach that apoE may be used therapeutically to protect against LPS-induced endotoxemia also known as sepsis and that lipopolysaccarides (LPS) are a component of gram-negative bacteria which is the primary cause of gram-negative sepsis.

Oosten et al., teach that all lipoproteins bind endotoxins and that combining lipoproteins with LPS before administration to mammals protects against endotoxin induced death (page 8820, col.2)

However Oosten et al, do not teach administering SEQ ID NO:11.

Applicant's position is that the finding by van Oosten et al. that apoE binds to the LPS of bacteria is not basis for predicting that apoC1 would have the same effect.

Not all apolipoproteins that have an effect on the lipid uptake in the liver have an effect on LPS binding (which is only logical considering that these are two different working mechanisms). This can be illustrated by the fact that one of the apolipoproteins, apoCIII, is able to inhibit the apoE-dependent

uptake of lipid particles in the liver but has no effect at all on sepsis related phenomena.

In his Table 1, Quarfordt et al. only show that combinations of apoCl and apoE have an effect on the uptake of lipid particles by liver cells. From this alone it is not possible to draw a conclusion about the effect of the individual components.

Even assuming arguendo, that this is the case, the effects of apoCl on uptake in liver cells is not predictive of the effects of apoCl in sepsis (or rather the immune response to toxic components of bacteria).

The working mechanism of apoC1 in sepsis is not through uptake (via an LDL receptor) as is the case with lipid uptake by the liver, but through binding to the toxic LPS of bacteria and the effects of this binding on the response generated via the TOLL-like receptor that mediates the immune response to these toxic components.

Further, although both apoE and apoC1 are apolipoproteins, they differ enormously:

1] they do not show a significant homology in their amino acid sequence,

2] apoE is 5 times as big as apoC1 and

3] the domains of apoE and apoC1 that bind to the LPS are completely different.

The direct teaching of van Oosten et al. as set forth above to a person skilled in the art is that apoE is able to bind the LPS of bacteria. But it would not be obvious to suggest that apoCl would have a similar effect.

First of all, the molecules differ too much to suggest a similar working mechanism based on structural similarities. Secondly, the publication of Quarfordt et al. would not be taken into consideration by a person of skill since the effects on liver uptake have nothing to do with the effects on sepsis. It is respectfully suggested the any suggestion of obviousness (which as demonstrated above is absent) could only be based on impermissible hindsight.

The examiner concludes that one of ordinary skill in the art would have a reasonable expectation of success by including apoCI within the composition of method of treatment because the art teaches the administration of ApoC1 and ApoE together.

The reasoning that leads from the disclosure of of the administration of ApoC1 and ApoE together to the conclusion that ApoCI is effective alone for a different purpose lacks basis in logic.

The art shows only that A and B together produce result X by a specific mechanism. There is no connection between that fact and the conclusion that A alone would produce result Y by a different mechanism.

The method of administration of apoCI and apoE as taught in the art is taught for an unrelated purpose, functioning through an unrelated biological pathway and thus there would be no motivation to try one or both of the components of the combination in response to a shock or sepsis condition. And since there would be no motivation to combine and experiment there would be not experimentation to find an appropriate

does since no does would have been though effective for sepsis or shock.

Claim appendix

1-16. Canceled

17. (Previously Presented) The method according to claim 27, wherein the mammal is a human.

18. (Previously Presented) The method according to claim 27, wherein the mammal is at risk of developing sepsis as a result of a surgical intervention or a weakened immune system.

19. (Withdrawn) A method for determining the severity of a septic condition and making a prognosis for the further course of the sepsis or septic shock in a mammal, or for monitoring a treatment of sepsis or septic shock in a mammal, which suffers from sepsis or septic shock, wherein the apoCI content is determined in a blood sample of the mammal.

20. (Withdrawn) The method according to claim 19, wherein the mammal is a human.

21. Cancelled

22. (Previously Presented) The method according to claim 27, wherein the peptide binds to lipoteichoic acids and wherein the composition is for preventing or treating a sepsis or septic shock in mammals.

23. (Previously Presented) The method according to claim 22, wherein the shock is caused by Gram-negative bacteria.

24. (Previously Presented) The method according to claim 23, wherein the mammal is a human, horse, cow, dog or cat.

25. (Previously Presented) The method according to claim 22, wherein the shock is caused by Gram-positive bacteria.

26. (Previously Presented) The method according to claim 25, wherein the mammal is a human, horse, cow, dog or cat.

27. (Previously Presented) A method for treating a mammal suffering from or is at risk of developing sepsis or septic shock comprising administering to such mammal a therapeutically effective amount of a peptide and pharmaceutically acceptably adjuvants where the peptide comprises an ~~the~~ amino acid sequence selected from SEQ ID NO.:11, SEQ ID NO.:2 and SEQ ID NO.:1.

28. (Previously Presented) The method of claim 27 where the peptide comprises the amino acid sequence of SEQ ID NO.:1.

29. (Withdrawn) A method of increasing the immune response produced in mammal by the presence of toxic components of bacteria by administering to such patient an immune response increasing amount of a peptide comprising the amino acid of SEQ ID NO.:11.

30. (Previously Presented) The method of claim 27 where the peptide comprises SEQ ID NO.:2.

31. (Previously Presented) The method of claim 27 where the peptide is the amino acid sequence of SEQ ID NO.:2.

32. (Previously Presented) The method of claim 32 where the mammal is a human.

33. (Withdrawn) A method of increasing the immune response produced in mammal by the presence of toxic components of bacteria by administering to such patient an immune response increasing amounts of a peptide of SEQ ID NO.:2.

Evidence appendix

None

Related proceedings appendix

None